## REMARKS

### I. Status of Claims

The instant invention presently contains Claims 1, 3-6, 19-22, 35 and 37.

Claims 2, 23-34 and 36 have been withdrawn.

Claims 1, 3-6, 19-22, 35 and 37 stand rejected.

The Examiner's remarks on cancellation of withdrawn claims are noted. Withdrawn claims will be cancelled when allowable subject matter is indicated.

### II. Amendment of Claims 1 and 38

The application is under final rejection. Permission is requested to amend the claims insofar as no further examination will be required thereby and/or the issues will be simplified for appeal.

Claims 1 and 38 have been amended to include the condition of "gas-free" to distinguish the instant invention from the gas-filled liposomes referenced in US. Pat. No 5,770,222 to Unger *et al.*, col. 5, lines 11-12 (at least 10% of the interior volume being gas). This amendment is a proper exclusion from claimed subject matter. See, *In re Johnson*, 558 F.2d 1008, 1017 (CCPA 1977) (the court should not let form triumph over substance by substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed.); *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993) (original disclosure conveys to one of ordinary skill in the art the absence of the excluded condition).

Claim 1 has been further amended to recite "consisting of" for "comprising."

### III. Claim Objections

The Examiner objected to claim 38 as to the phrase "comprising the steps of." Applicant has amended Claim 38 accordingly to clarify a second step. Applicant believes that this objection is met.

## IV. Claims 38, 40 and 42 are rejected under 35 USC § 102(b)

The Examiner initially rejected claims 38, 40 and 42 under 35 USC § 102(e) as being anticipated by U.S. Patent No. 7,008,791 to Gregoriadis *et al.*, ("Gregoriadis"). However, in discussion with Thomas M. Saunders on July 16, and 17, 2009, the Examiner indicated that 35 USC § 102(b) would also have been a basis for rejection if the international publication had been cited as the basis of rejection. Applicant respectfully traverses this rejection. The courtesy of Examiner Nguyen's telephone calls are gratefully acknowledged.

### A. The Rejection:

Gregoriadis is presented as disclosing various cationic lipid components, cholesterol and entrapping "a DNA encoding an antigen," "nucleic acid may be complexed with liposomes," and "the nucleic acid is at least partially entrapped." Office Action of May 1, 2009, page 4, last paragraph. Further the Examiner states that "The teachings of Gregoriadis et al meet every limitation of the instant claims as written. Office Action of May 1, 2009, page 5, second paragraph.

### B. Applicant's Invention:

Applicant claims "depot system, for delayed release of active substances." Applicant respectfully emphasizes (i) delayed release is a claimed feature and that (ii) proteins and peptides are not nucleic acids.

### The Deficiency of Gregoriadis:

Gregoriadis does not teach delayed release. Gregoriadis does not teach the use of claimed "protein or peptide active" substances. Gregoriadis is not and cannot be anticipatory of the claimed invention. Applicant requests that the rejection be withdrawn.

## V. Claims 38 through 43 are rejected under 35 USC § 102(b)

The Examiner rejected claims 38 through 43 under 35 USC § 102(b) as being anticipated by U.S. Patent No. 5,770,222 to Unger *et al.*, ("Unger"). Applicant respectfully traverses this rejection.

### A. The Rejection:

Unger is cited as a drug delivery system with gas-filled liposomes and some level of impermeability. Unger is also cited for having "at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their

impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied." Office Action of May 1, 2009, at 5.

**B. Applicant's Invention:**

Applicant's invention is a depot system claiming "*delayed* release of active substances." "Delayed release" as the term is used by Applicant references "depot systems which avoid 'burst release' of active substance or, if therapeutically indicated, achieve rapid initial partial release of active substance, followed by a sustained release of active substance." Specification, ¶15. This presents two aspects. First, there is no burst release." Second, even if there is a rapid initial release of drug, it is followed by a long release profile.

As amended, Claim 38 includes the condition of "gas-free" as does Claims 39 through 43 dependent on Claim 38. It is proper to exclude gas filled liposomes by amendment. See, *In re Johnson*, 558 F.2d 1008, 1017 (CCPA 1977) (the court should not let form triumph over substance by substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed); *Ex parte Parks,* 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993) (original disclosure conveys to one of ordinary skill in the art the absence of the excluded condition).

**C. The Deficiency of Unger**

Unger is not a "delayed release" system as the term is used by the Applicant. The claimed "delayed release" excludes burst release. It is respectfully submitted that rejection based on Unger improperly views *no release* followed by a *burst release* as being equivalent to Applicant's claimed delayed release depot system. This is not accurate and is inconsistent with the plain statements of both Unger and Applicant. Unger discloses having "at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied" – nothing but burst. Unger's burst release condition is emphasized with reference to Unger, col. 2, lines 12-17:

> Once the microspheres have been introduced into the patient's body, a therapeutic compound may be targeted to specific tissues through the use of sonic energy, which is directed to the target area and causes the *microspheres* to *rupture* and release the therapeutic compound. (emphasis added)

And col. 2, lines 22-2:9

> The invention also contemplates methods for the *controlled delivery* of therapeutic compounds to a region of a patient comprising: (i) administering to the patient gas-filled microspheres comprising a therapeutic compound; (ii) monitoring the microspheres using ultrasound to determine the presence of the microspheres in the region; and (iii) *rupturing the microspheres using ultrasound to release the therapeutic compound in the region.* (emphasis added)

Unger's "controlled delivery" is not Applicant's "delayed release." Rupture of the liposomes can only result in burst release without the possibility of a continuing release.

As amended, Claims 38 through 43 are distinct and not anticipated by Unger. The teaching of Unger is contrary to the claimed depot system of Applicant. Further, Unger fails as a single source disclosing all of the claimed elements arranged as in the claim. *Richardson v. Suzuki Motor Co.* 886 F 2d 1226, 1239 (Fed.Cir. 1989). Applicant requests that the rejection be withdrawn.

## VI. Obligations under 37 CFR § 1.56

Applicant notes and acknowledges the obligations cited by the Examiner as to 37 CFR § 1.56. Further comment is deemed unnecessary.

## VII. Claims 1, 3 through 6, 19 through 22, 35 and 37 are rejected under 35 USC § 103(a)

The Examiner rejected 1, 3 through 6, 19 through 22, 35 and 37 under 35 USC § 103(a) as unpatentable over Unger in view of Gregoriadis. Applicant respectfully traverses this rejection.

### A. Examiner's Rejection:

The Examiner's rejection states that Unger already disclosed a drug delivery system comprising gas-filled liposomes having encapsulated therein a therapeutic drug, wherein at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied. The Examiner further states that Unger also teaches that the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation and the lipid in the gas-filled liposomes may be in the form a single bilayer or a multilamellar bilayer and that utilized lipids to create liposome microspheres include and not

limited to lipids such as DMPC, DPPC, DSPC cholesterol, cholesterol sulfate and cholesterol hemisuccinate and if desired a variety of cationic lipids.

The Examiner acknowledges that Unger does not teach specifically the preparation of a liposome comprising saturated synthetic phosphatidyl cholines selected from the group consisting of DMPC, DPPC and DSPC; cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of DC-Chol, DAC-Chol, DMTAP, DPTAP and DOTAP with a percentage ranging from about 5 to 20 mole-% and one or more selected from the group consisting of protein and peptide active substances.

The Examiner believes that the deficiencies in Unger, acknowledged above, in arriving at Applicant's claimed invention are cured by Gregoriadis. The Examiner reasons that Gregoriadis already disclosed at least a liposome preparation comprising at least a cationic compound such as DOTP or DC-Chol, at least one zwitterionic phospholipids such as DPPC and DSPC and cholesterol, wherein the amount of cationic compound is preferably in the range of 5 to 50% of the total moles of liposome forming components. The Examiner further stated that Gregoriadis further taught that the product liposomes may be multilamellar or unilamellar vesicles.

**B. Applicants' Claimed Invention:** As noted above, Applicant's claimed invention is to a delayed release depot system. Furthermore, as described in amended independent Claims 1 from which claims 3 through 6, 19 through 22, 35 and 37 depend, now requires (i) gas-free liposomes and (ii) depot system having "saturated synthetic phosphatidyl cholines selected from one or more from the group consisting of dimyristoyl phosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC) and distearoyl phosphatidylcholine (DSPC), cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of 3-β-[N-(N',,N'-dimethylaminoethane)carbamoyl]cholesterol (DC-Chol), 3-β-[N-(N,,N'-dimethylaminoethane)carbamoyl]cholesterol (DAC-Chol), N-[1-(2,3-dimyristoyloxy)propyl]-N, N, N-trimethylammonium salt (DMTAP), N-[1-(2,3-dipalmitoyloxy)propyl]-N, N, N-trimethylammonium salt (DPTAP) and N-[1-(2,3-dioleoyloxy)propyl]-N, N, N-trimethylammonium salt (DOTAP) with a percentage ranging from 5 to 20 mole-% in the liposomal membrane, and one or more selected active substances from the group consisting of protein and peptide active substances."

**C. Teachings of Cited References:**

**Unger:** Unger discloses a burst release system incompatible with the claimed delayed

release depot system. Unger's gas-filled liposome compositions and drugs encapsulated therein are employed with ultrasonic energy interacts with a gas within a gas-filled microspheres resulting in a burst of the microspheres. This results in immediate therapeutic agent released without the possibility of any extended release. Unger teaches only a one shot release.

As to specific components, we note that the examples contained within Unger liposomes from DPPC or DPPC/DOTMA or PEG-DPPE or eggPC/DOTMA or DPPC/sodium lauryl sulphate or DSPC were used. Unlike the instant claimed invention, the disclosed specific liposome compositions of Unger do not comprise cholesterol and the presence of cationic lipids is not mandatory. Furthermore Unger teaches the materials that may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation.

**Gregoriadis:** Gregoriadis discloses oral vaccines comprising a nucleic acid coding for an antigen against which vaccination is desired. Gregoriadis found that liposomal compositions as oral vaccines preferably comprising at least one zwitterionic phospholipid and at least one cationic compound. In a preferred aspect of the invention the zwitterionic phospholipid is a mixture of DSPC and DOPE, a saturated phosphatidylcholine and an unsaturated phosphatidylethanolamine (col. 3, line 15-18). Gregoriadis also mentioned that other components may be included in the liposome forming component, such as cholesterol in amounts up to 50 % by weight. However, Gregoriadis teaches that the liposome forming components are preferably free of cholesterol (see col.4, line 18-19 or Example 2 (col. 8, line 67 – col. 9, line 1-3). Accordingly, the liposomal compositions of Gregoriadis are free of cholesterol.

D. **Deficiencies of the References:**

**Unger:** Unger is a burst release system and not a delayed release system. Unger offers no more than a generic disclosure of lipids suitable to make liposomes and drugs encapsulated therein. In the context of the earlier § 102(a) rejection, the Examiner presents Unger and quotes col.7, lines 42-44:

> "**materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation.**" (emphasis in original) Office Action of May 1, 2009, page 5, last paragraph.

This general statement is followed by a partial quotation from Unger col. 7, line 55 through col. 8, line 32. Applicant sets forth that section of Unger in full:

> Lipids which may be used to create liposome microspheres include but are not limited to: lipids such as fatty acids, lysolipids, phosphatidylcholine with both saturated and unsaturated lipids including dioleoylphosphatidylcholine; dimyristoylphosphatidylcholine; dipentadecanoylphosphatidylcholine, dilauroylphosphatidylcholine, dipalmitoylphosphatidylcholine; distearoylphosphatidylcholine; phosphatidylethanolamines such as dioleoylphosphatidylethanolamine; phosphatidylserine; phosphatidylglycerol; phosphatidylinositol, sphingolipids such as sphingomyelin; glycolipids such as ganglioside GM1 and GM2; glucolipids; sulfatides; glycosphingolipids; phosphatidic acid; palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers such as polyethyleneglycol, chitin, hyaluronic acid or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol sulfate and cholesterol hemisuccinate; tocopherol hemisuccinate, lipids with ether and ester-linked fatty acids, polymerized lipids, diacetyl phosphate, stearylamine, cardiolipin, phospholipids with short chain fatty acids of 6-8 carbons in length, synthetic phospholipids with asymmetric acyl chains (e.g., with one acyl chain of 6 carbons and another acyl chain of 12 carbons), 6-(5-cholesten-3.beta.-yloxy)-1-thio-.beta.-D-galactopyranoside, digalactosyldiglyceride, 6-(5-cholesten-3.beta.-yloxy)hexyl-6-amino-6-deoxy-1-thio-.beta.-D-galacto pyranoside, 6-(5-cholesten-3.beta.-yloxy)hexyl-6-amino-6-deoxyl-1-thio-.alpha.-D-manno pyranoside, 12-(((7'-diethylaminocoumarin-3-yl)carbonyl)methylamino)-octadecanoic acid; N-[12-(((7'-diethylaminocoumarin-3-yl)carbonyl)methyl-amino) octadecanoyl]-2-aminopalmitic acid; cholesteryl)4'-trimethyl-ammonio)butanoate; N-succinyldioleoylphosphatidylethanolamine; 1,2-dioleoyl-sn-glycerol;1,2-dipalmitoyl-sn-3-succinylglycerol; 1,3-dipalmitoyl-2-succinylglycerol;1-hexadecyl-2-palmitoylglycerophosphoet hanolamine and palmitoylhomocysteine, and/or combinations thereof.
>
> If desired, a variety of cationic lipids such as DOTMA, N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammoium chloride; DOTAP, 1,2-dioleoyloxy-3-(trimethylammonio)propane; and DOTB, 1,2-dioleoyl-3-(4'-trimethyl-ammonio)butanoyl-sn-glycerol may be used. In general the molar ratio of cationic lipid to non-cationic lipid in the liposome may be, for example, 1:1000, 1:100, preferably, between 2:1 to 1:10. . . Unger col. 7, line 55 through col. 8, line 32.

Advancing this wholesale litany of possible liposomal constituents is an improper basis for rejection. Unger represents the archetypal non-obviating "basket disclosure." *In re Ruschig*, 343 F 2d 965 (CCPA 1965). Nothing in Unger directs one skilled in the art to the claimed selection of liposome forming agents nor excludes unsuitable agents. Unger cannot be read as

teaching or suggesting a delayed release depot system. As claimed, the liposomes are formed of saturated synthetic phosphatidyl cholines selected from one or more from the group consisting of dimyristoyl phosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC) and distearoyl phosphatidylcholine (DSPC), cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of 3-β-[N-(N',,N'-dimethylaminoethane)carbamoyl]cholesterol (DC-Chol), 3-β-[N-(N,,N'-dimethylaminoethane)carbamoyl]cholesterol (DAC-Chol), N-[1-(2,3-dimyristoyloxy)propyl]-N, N, N-trimethylammonium salt (DMTAP), N-[1-(2,3-dipalmitoyloxy)propyl]-N, N, N-trimethylammonium salt (DPTAP) and N-[1-(2,3-dioleoyloxy)propyl]-N, N, N-trimethylammonium salt (DOTAP) with a percentage ranging from 5 to 20 mole-% in the liposomal membrane.

The disclosed specific liposome compositions of Unger do not comprise cholesterol and the presence of cationic lipids is not mandatory. The instant claimed invention comprises saturated phospholipids, such as DSPC, DPPC or DMPC and cholesterol or derivatives and cationic lipids such as DC-Chol, DAC-Chol, DMTAP, DPTAP and/or DOTAP, which are useful as delayed release depot systems for the sustained release of active agents. This is inconsistent with the teaching of Unger. Here, the presence of cationic lipid is mandatory.

Separately or combined, the teachings of Unger and Gregoriadis do not reach the claimed delayed release depot system absent improper picking and choosing and improper hindsight reconstruction of Applicant's invention. Applicant respectfully requests that the rejected claims be withdrawn.

**Conclusion**

Applicant believes that the foregoing response has placed the application in condition for allowance which is promptly requested.

Please charge any deficiency as well as any other fees which may become due at any time during the pendency of this application, or credit any overpayment of such fees to deposit account No. 02-3038. Also, in the event any extensions of time for responding are required for the pending application, please treat this paper as a petition to extend the time as required and charge Deposit Account No. 02-3038.

Respectfully submitted,

Dated: August 31, 2009

/Thomas M. Saunders /
Thomas M. Saunders, Reg. No.: 29,585
Customer No. 21127
Attorney for Applicant(s)
RISSMAN HENDRICKS & OLIVERIO LLP
100 Cambridge Street
Suite 2101
Boston, MA 02114
Tel: 617-933-4442
Fax: 617-367-4656
E-mail: tsaunders@rhoiplaw.com